

We claim:

1. An analog of a protein regulating complement activation having short consensus repeats of amino acid sequence selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, and these complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein said protein analog is selected from the group consisting of complement regulating proteins containing short consensus repeats derived from a second, different complement regulating protein, complement regulating proteins wherein the short consensus repeats are rearranged, complement regulating proteins having defined amino acid substitutions in the short consensus repeats selected from the group consisting of repeats having binding activity, cofactor activity, and decay accelerating activity, wherein the substitution alters the activity of the naturally occurring complement regulatory protein, and complement regulating proteins consisting of as few as three short consensus repeats, wherein the protein has complement regulatory activity.

2. The analog of claim 1 wherein the complement regulatory activity is selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, C4b cofactor activity, and decay accelerating activity.

3. The analog of claim 2 wherein the protein is complement receptor one.

4. The analog of claim 2 wherein the protein is decay accelerating factor.

5. The analog of claim 2 wherein the protein is factor H.

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B2

sub
C3

sub
D2

6. The analog of claim 2 wherein the C3b binding and cofactor activities of the protein are enhanced by substitutions increasing C4b binding of the protein.

7. The analog of claim 2 wherein the C4b binding and cofactor activities of the protein are enhanced by substitutions increasing C3b binding of the protein.

8. The analog of claim 2 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:

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CR1-4 with its first 122 amino acids (SCR1-2) replaced with CR1 amino acids 497-618 (SCR 8-9) and CR1-4(8,9) with deletion of 194-253; substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K, or structurally similar amino acids.

9. The analog of claim 2 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:

79: D; 37,39: Y,D; 92: T; 109-112: N-A-A-H; 109-112, 114-117, 121: N-A-A-H, S-T-K-P...Q; 114-117, 121: N-A-A-H, S-T-K-P...Q; 116: K; 116,117: K-P; 92-94: K...Y; 99,103,106: S...T...I; 109-112: P-T-V-I; 110: T; 111: V; 112: I; 114: D; 115: N; 121: D; 117: T; 1,3: Q...N; 6-9: E-W-L-P; 12-16, 18-21: K-L-K-T-Q...N-A-S-D; 27,29: S...K; 37: S; 44, 47, 49: I...K...S; 52-54, 57, 59: T-G-A...R...R; 78-79, 82: K-G...F; 85, 87: Q...K; 12-16, 18-21: R-P-T-N-L...D-E-R-E; 27,29: Y...N; 35, 64-65, 94: G...R-N...Y, substitutions with structurally similar amino acids, and combinations thereof.

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10. The analog of claim 2 wherein the complement regulatory protein is decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 selected from the group consisting of 180-187: S-T-K-P-P-I-C-Q; 175-178: N-A-A-H; 175-187: S-T-K-P-P-I-C-Q-N-A-A-H; 130: R; 145: D; 77-84: K-L-K-T-Q-T-N-A-S-D; 90-92: S-L-K, substitutions with structurally similar amino acids, and combinations thereof.

11. The analog of claim 1 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

12. The analog of claim 1 comprising at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H.

Sub B³

13. The analog of claim 1 wherein the protein comprises C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

Sub C⁵

14. The analog of claim 1 wherein the protein consists essentially of three short consensus regions and has two complement regulatory activities.

15. The analog of claim 1 further comprising a pharmaceutically acceptable carrier for administration to a patient in need thereof.

16. A method for making an analog of a protein regulating complement activation having short consensus repeats of amino acid sequence selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, and these complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein said protein analog is selected from the group consisting of complement regulating proteins containing short consensus repeats derived from a second, different complement regulating protein, complement regulating proteins wherein the short consensus repeats are rearranged, complement regulating proteins having defined amino acid substitutions in the short consensus repeats selected from the group consisting of repeats having binding activity, cofactor activity, and decay accelerating activity, wherein the substitution alters the activity of the naturally occurring complement regulatory protein, and complement regulating proteins consisting of as few as three short consensus repeats, wherein the protein has complement regulatory activity.

Sub B4

17. The method of claim 16 wherein the complement regulatory activity is selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, C4b cofactor activity, and decay accelerating activity.

Sub C6

18. The method of claim 16 wherein the protein is complement receptor one.

Sub D7

19. The method of claim 16 wherein the protein is decay accelerating factor.

20. The method of claim 16 wherein the protein is factor H.

21. The method of claim 17 wherein the C3b binding and cofactor activities of the protein are enhanced by substitutions increasing C4b binding of the protein.

22. The method of claim 17 wherein the C4b binding and cofactor activities of the protein are enhanced by substitutions increasing C3b binding of the protein.

23. The method of claim 17 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:

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CR1-4 with its first 122 amino acids (SCR1-2) replaced with CR1 amino acids 497-618 (SCR 8-9) and CR1-4(8,9) with deletion of 194-253; substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K, or structurally similar amino acids.

24. The method of claim 17 wherein the protein contains a change within a short consensus repeat that corresponds with a change to complement receptor one selected from the group consisting of:

79: D; 37,39: Y,D; 92: T; 109-112: N-A-A-H; 109-112, 114-117, 121: N-A-A-H, S-T-K-P...Q; 114-117, 121: N-A-A-H, S-T-K-P...Q; 116: K; 116,117: K-P; 92-94: K...Y; 99,103,106: S...T...I; 109-112: P-T-V-I; 110: T; 111: V; 112: I; 114: D; 115: N; 121: D; 117: T; 1,3: Q...N; 6-9: E-W-L-P; 12-16, 18-21: K-L-K-T-Q...N-A-S-D; 27,29: S...K; 37: S; 44, 47, 49: I...K...S; 52-54, 57, 59: T-G-A...R...R; 78-79, 82: K-G...F; 85, 87: Q...K; 12-16, 18-21: R-P-T-N-L...D-E-R-E; 27,29: Y...N; 35, 64-65, 94: G...R-N...Y, substitutions with structurally similar amino acids, and combinations thereof.

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Concl.

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25. The method of claim 17 wherein the complement regulatory protein is decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 selected from the group consisting of 180-187: S-T-K-P-P-I-C-Q; 175-178: N-A-A-H; 175-187: S-T-K-P-P-I-C-Q-N-A-A-H; 190: R; 145: D; 77-84: K-L-K-T-Q-T-N-A-S-D; 90-92: S-L-K, substitutions with structurally similar amino acids, and combinations thereof.

26. The method of claim 16 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

27. The method of claim 16 comprising at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H.

28. The method of claim 16 wherein the protein comprises C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

29. The method of claim 16 wherein the protein consists essentially of three short consensus regions and has two complement regulatory activities.

30. The method of claim 16 further comprising mixing with the analog a pharmaceutically acceptable

Sub C8

Sub B5

Deekh FG

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John E8
carrier for administration to a patient in need
thereof.

John E8
31. A DNA sequence which encodes the analogs
of claim 1.

John E8
32. The DNA sequence of claim 31 in an
expression system which is capable, when transformed
into a compatible recombinant host cell, of expressing
a DNA encoding the analog of claim 1; the expression
system comprising a DNA encoding the analog operably
linked to control sequences compatible with the host.

John E8
33. The DNA sequence of claim 31 stably
incorporated into the genome of a transgenic animal.

John E8
34. A method for enhancing the C4b or C3b
cofactor activity of a complement regulatory protein,
wherein the protein has either C3b or C4b cofactor,
comprising adding sequences to the protein conferring
binding of the other ligand, either C4b or C3b.

John E8
B6

John E8
B7